Cancer Cell
Previews

Targeting Tumor Architecture to Favor Drug Penetration: A New Weapon to Combat Chemoresistance in Pancreatic Cancer?

Man Yu[1] and Ian F. Tannock[1,2,*]
[1]Ontario Cancer Institute/Princess Margaret Hospital, University Health Network and University of Toronto, Toronto, ON M5G 2M9, Canada
[2]Division of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network and University of Toronto, Toronto, ON M5G 2M9, Canada
*Correspondence: ian.tannock@uhn.ca
DOI 10.1016/j.ccr.2012.03.002

Pancreatic ductal adenocarcinoma (PDA) responds poorly to chemotherapy. In this issue of *Cancer Cell*, Provenzano et al. identify hyaluronan as a pivotal determinant of elevated interstitial fluid pressures (IFP) and vascular collapse in PDA. PEGPH20 treatment ablates stromal hyaluronan, normalizes IFP, and increases accessibility of tumor cells to anticancer drugs.

Pancreatic ductal adenocarcinoma (PDA) is among the most lethal human malignancies due to its insidious onset and resistance to therapy. Most anticancer drugs, including standard-of-care gemcitabine and novel molecular targeted therapies that have displayed impressive activity against PDA cells in culture and in some preclinical animal models, yield little success in the clinic (Li et al., 2010). Sensitivity of neoplastic cells in such models is a poor predictor of clinical effectiveness.

In addition to epigenetic and genetic alterations in cancer cells that influence drug sensitivity, the tumor microenvironment mediates responses of solid tumors to chemotherapy (Trédan et al., 2007). The vasculature of solid tumors is disorganized compared to that in normal tissues, with variable blood flow and large distances between functional capillaries. This leads to gradients from tumor blood vessels of nutrients, with regions of hypoxia and extracellular acidity and gradients in tumor cell proliferation (Figure 1). Anticancer drugs are delivered through blood vessels, and gradients in their concentration are established within tumors; cells distal from blood vessels are likely to be resistant to systemic therapy because of low drug concentration and because most drugs, including many targeted agents, are more active against rapidly-proliferating cells. A dense extracellular matrix (ECM) and stromal components of tumors increase interstitial fluid pressure (IFP), which limits ability of larger molecules, including therapeutic antibodies, to penetrate tumor tissue by convection; if IFP exceeds capillary pressure, vascular collapse will occur, limiting delivery of all drugs (and nutrients) to the tumor. The above factors are particularly relevant to PDA, which usually has a dense desmoplastic stroma with fibrotic connective tissue that surrounds the tumor and may account for >80% of tumor volume (Erkan et al., 2010). This leads to a microenvironment with low blood perfusion and hypoxia, serving as a "wall-like" barrier to diminish the delivery of anticancer drugs and stimulating aggressive tumor cell behavior (Neesse et al., 2011). The amount of reactive stroma is an independent predictor for poor prognosis of patients with PDA (Erkan et al., 2008). Hence, targeting non-neoplastic components within the microenvironment provides an opportunity for developing more effective therapies.

In this issue of *Cancer Cell*, Provenzano et al. (2012) characterize histologically various stromal components in preinvasive, invasive, and metastatic pancreatic tissues in mice and humans. They and others have shown that autochthonous PDA in $Kras^{LSL\text{-}G12D/+}$;*Cre* and $Kras^{LSL\text{-}G12D/+}$;$Trp^{53LSL\text{-}R172H/+}$;*Cre* conditional knockout mice provide excellent models for human PDA (see also Olive et al., 2009). Provenzano and colleagues demonstrate that the content of collagen and glycosaminoglycans increases progressively with histopathological grade from early precusor lesions to invasive and metastatic PDA tumors. The expression and abundance of hyaluroic acid (HA), a large linear glycosaminoglycan associated with inflammation, wound repair, and tissue remodelling (Toole, 2004), are elevated during carcinogenesis. These findings, along with similar observations in other solid tumors (Toole, 2004), suggest that accumulation of HA contributes to neoplastic transformation, tumor progression, and drug resistance in PDA. Using three-dimensional matrices, the investigators demonstrate that the presence of HA can directly elevate IFP. The authors measure IFP in murine PDA and find a range of 75–130 mm Hg, much larger than values in the normal pancreas or than capillary blood pressure (range: 8–13 mm Hg). These extremely high levels of IFP induce vascular collapse and limit availability of drugs to the tumor.

In this issue of *Cancer Cell*, Provenzano et al. (2012) then evaluate intravenous administration of PEGPH20, a HA-targeting enzymatic agent, in mice bearing autochtonous PDA. PEGPH20 depletes HA in the tumor matrix, resulting in a marked reduction in IFP, increased diameter of $CD31^{+}$ blood vessels, increased patent vessels, and improved penetration of doxorubicin in PDA. They compare treatment with gemcitabine with or without PEGPH20 in cohorts of mice bearing autochtonous PDA. Gemcitabine alone has negligible effects, but the combination leads to reduced tumor size and increased apoptosis of tumor cells with all tumors responding after three cycles. Combined treatment decreases metastatic tumor burden and increases overall

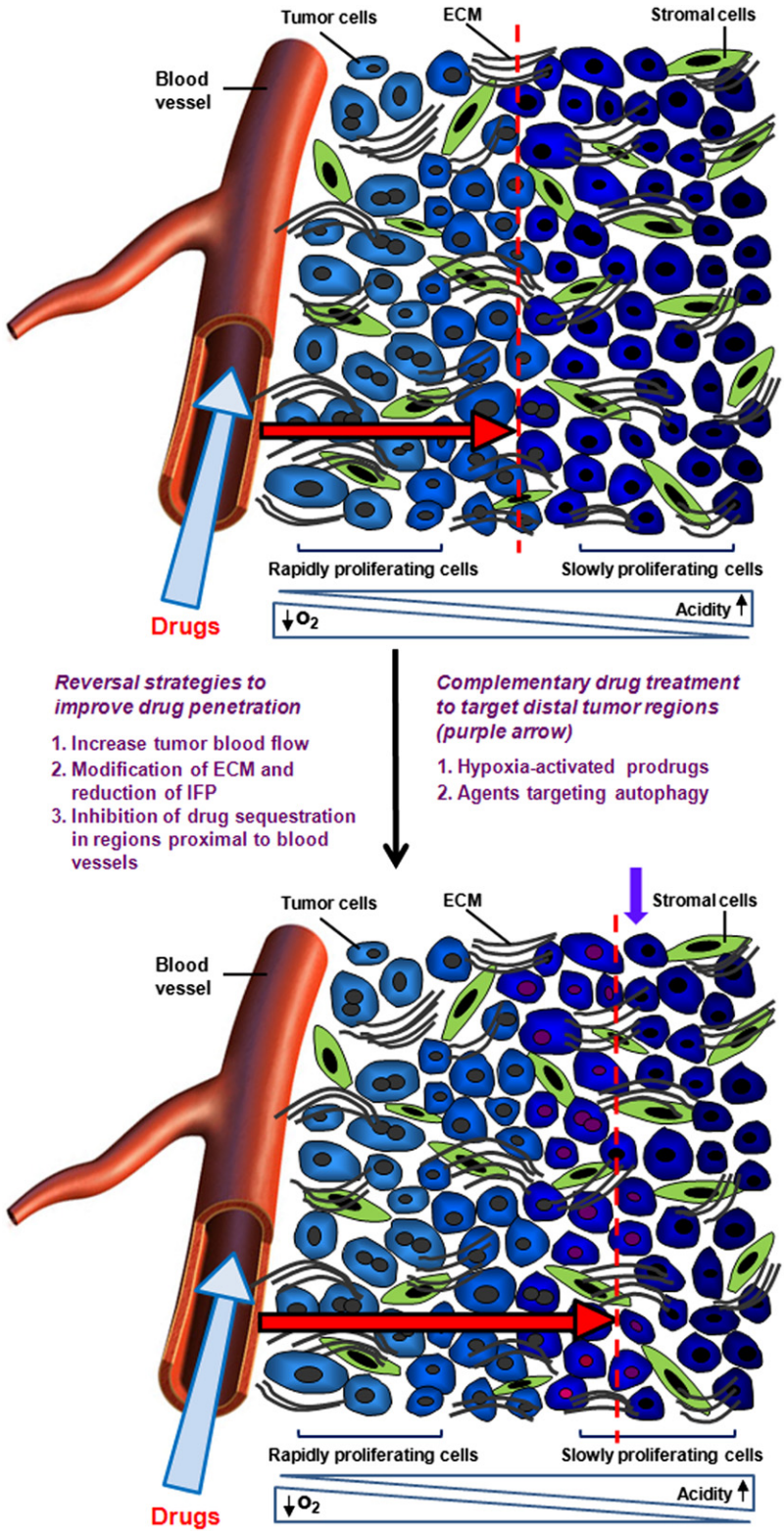

Figure 1. Strategies to Overcome the Effects of Limited Drug Distribution in Solid Tumors
Drug distribution in solid tumors is determined by various factors including molecular size and charge, consumption of drugs by cells proximal to blood vessels, and the volume and organization of the extracellular matrix (ECM). As shown by Provenzano et al. (2012), modification of the ECM can lead to a decrease of high interstitial fluid pressure (IFP) and an increase of tumor blood flow, allowing greater access of cytotoxic agents to tumor cells. Other strategies to improve drug distribution (indicated schematically by red arrows and dashed lines) include augmentation of tumor blood flow and inhibition of drug sequestration in cells close to blood vessels. Combined treatment with conventional therapeutics and drugs that both diffuse to and target cells distant from blood vessels (e.g., hypoxia-activated prodrugs and agents that target autophagy) may also improve therapeutic effectiveness.

survival of animals when compared to either agent used alone. These therapeutic effects are accompanied by extensive remodeling of tumor stroma and maintainance of a functional vasculature. In light of these promising results and encouraging data from phase I clinical trials, a phase II trial has been intitiated to investigate the effects of gemcitabine + PEGPH20 in the treatment of patients with advanced, previously-untreated PDA (http://www.clinicaltrials.gov).

Other investigators have used strategies to improve vascular perfusion and drug delivery in PDA. Olive et al. (2009) reported that depletion of tumor-associated stromal fibroblasts by disrupting Hedgehog signaling increased intratumoral vascular density transiently via neoangiogenesis and resulted in improved delivery and greater antitumor activity of gemcitabine using the same mouse model of PDA. Two drugs that inhibit the Hedgehog pathway (GDC-0449 and LDE225) are being evaluated with chemotherapy in phase II clinical trials for PDA (http://www.clinicaltrials.gov).

Will these strategies translate into improved outcome for people with advanced PDA? Targeting the tumor microenvironment is an innovative approach worthy of study in cinical trials, especially for a disease where other strategies have yielded only minor improvements in outcome. However, all mice in the preclinical trials conducted by Provenzano et al. (2012) eventually die of their tumors. Even if enzymatic treatment can lead to vascular remodeling and increased perfusion in human PDA, there remain gradients in drug concentration in relation to tumor blood vesseels and resistance of poorly-nourished slowly-proliferating cells to anticancer drugs, a problem common to solid tumors (Trédan et al., 2007). As shown by Huxham et al. (2004), tumor repopulation is intiated from cells distant from blood vessels when transplanted

human colorectal xenografts are treated with gemcitabine.

The major contributions of Olive et al. (2009) and Provenzano et al. (2012) are in demonstrating the importance of the microenvironment of PDA, and of solid tumors in general, in determining resistance to drug therapy. The majority of research on drug resistance has concentrated on molecular properties of individual cancer cells. Although intrinsic sensitivity is important, it is only part of the story—stated simply, if a drug does not get to some of the tumor cells, they will not be killed no matter how sensitive they might be to the drug in cell culture. More research should focus on strategies that recognize the importance of the tumor microenvironment and drug delivery in limiting therapeutic efficacy. There are several approaches to this problem, some of which are outlined in Figure 1. They include strategies to target the ECM with enzymes such as PEGPH20 or inhibition of Hedgehog signaling, strategies to decrease drug sequestration in cells proximal to blood vessels thereby allowing better distribution of drugs to distal cells, and combination treatment using "conventional" therapeutics together with drugs that both diffuse to and target specifically cells distant from blood vessels. Promising drugs for the latter include hypoxia-activated prodrugs and agents that attack the process of autophagy, a survival mechanism for stressed tumor cells (Trédan et al., 2007; Yang et al., 2011).

In summary, the efficiency of systemic chemotherapy for PDA in particular and for solid tumors in general is hindered by poor delivery of drugs to some tumor regions and by effects of the tumor microenvironment on drug activity. As Provenzano and coworkers show convincingly, agents that improve drug delivery by modifying factors relating to the tumor microenvironment represent an important future direction for cancer therapy.

REFERENCES

Erkan, M., Michalski, C.W., Rieder, S., Reiser-Erkan, C., Abiatari, I., Kolb, A., Giese, N.A., Esposito, I., Friess, H., and Kleeff, J. (2008). Clin. Gastroenterol. Hepatol. *6*, 1155–1161.

Erkan, M., Reiser-Erkan, C., Michalski, C.W., and Kleeff, J. (2010). Exp. Oncol. *32*, 128–131.

Huxham, L.A., Kyle, A.H., Baker, J.H., Nykilchuk, L.K., and Minchinton, A.I. (2004). Cancer Res. *64*, 6537–6541.

Li, J., Wientjes, M.G., and Au, J.L. (2010). AAPS J. *12*, 223–232.

Neesse, A., Michl, P., Frese, K.K., Feig, C., Cook, N., Jacobetz, M.A., Lolkema, M.P., Buchholz, M., Olive, K.P., Gress, T.M., and Tuveson, D.A. (2011). Gut *60*, 861–868.

Olive, K.P., Jacobetz, M.A., Davidson, C.J., Gopinathan, A., McIntyre, D., Honess, D., Madhu, B., Goldgraben, M.A., Caldwell, M.E., Allard, D., et al. (2009). Science *324*, 1457–1461.

Provenzano, P.P., Cuevas, C., Chang, A.E., Goel, V.K., Von Hoff, D.D., and Hingorani, S. (2012). Cancer Cell *21*, this issue, 418–429.

Toole, B.P. (2004). Nat. Rev. Cancer *4*, 528–539.

Trédan, O., Galmarini, C.M., Patel, K., and Tannock, I.F. (2007). J. Natl. Cancer Inst. *99*, 1441–1454.

Yang, Z.J., Chee, C.E., Huang, S., and Sinicrope, F.A. (2011). Mol. Cancer Ther. *10*, 1533–1541.

A Tell-Tail Sign of Chromatin: Histone Mutations Drive Pediatric Glioblastoma

Esther Rheinbay,[1,2,3,4] David N. Louis,[2] Bradley E. Bernstein,[1,2,3,*] and Mario L. Suvà[1,2,3]
[1]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
[2]Department of Pathology, Center for Cancer Research, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[3]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA
[4]Bioinformatics Program, Boston University, Boston, MA 02215, USA
*Correspondence: bernstein.bradley@mgh.harvard.edu
DOI 10.1016/j.ccr.2012.03.001

Recent genomic analyses of pediatric glioblastoma, a poorly understood tumor with dismal outcome, have identified mutations in histone H3 variants that affect critical amino acids in the tail. The findings extend discoveries of chromatin regulator inactivation and gain-of-function mutations by documenting alteration of a modifiable histone residue in human cancer.

Brain tumors are the most common solid neoplasms of childhood and the primary cause of cancer-related deaths in children. Although their pathological classification is complex, most high-grade brain tumors in children are categorized as either embryonal (such as medulloblastoma) or glial (such as the diffusely infiltrative glioblastoma [GBM]). An anatomical variant of high-grade glioma, diffuse intrinsic pontine glioma (DIPG), is a particularly vexing clinical challenge given its location in the neurologically critical brain stem. Over the past few decades, major progress has been made in the understanding and treatment of children with medulloblastomas, but little real progress has been made in the treatment of children with malignant diffuse gliomas. Consistent prognostic estimates have been difficult to establish, since the clinical behavior of childhood diffuse gliomas is not as stereotypical as that of their more common adult counterpart.